

i. Animals with pancreatic b-cells destroyed by specific chemical cytotoxins such as

A 21 Alloxan or Streptozotocin (e.g. the Streptozotocin-treated mouse, -rat, dog, and -monkey).
 Kodama, H., Fujita, M., Yamaguchi, I., *Japanese Journal of Pharmacology* 1994, 66, 331-336
 (mouse); Youn, J.H., Kim, J.K., Buchanan, T.A., *Diabetes* 1994, 43, 564-571 (rat); Le
 Marchand, Y., Loten, E.G., Assimacopoulos-Jannet, F., et al., *Diabetes* 1978, 27, 1182-88 (dog);
 and Pitkin, R.M., Reynolds, W.A., *Diabetes* 1970, 19, 70-85 (monkey).

At page 91, please replace the paragraph beginning on line 24 with the following paragraph:

A 22 *A 23* *A 24* *A 25* *A 26* *A 27* *A 28* *A 29* *A 30* *A 31* *A 32* *A 33* *A 34* *A 35* *A 36* *A 37* *A 38* *A 39* *A 40* *A 41* *A 42* *A 43* *A 44* *A 45* *A 46* *A 47* *A 48* *A 49* *A 50* *A 51* *A 52* *A 53* *A 54* *A 55* *A 56* *A 57* *A 58* *A 59* *A 60* *A 61* *A 62* *A 63* *A 64* *A 65* *A 66* *A 67* *A 68* *A 69* *A 70* *A 71* *A 72* *A 73* *A 74* *A 75* *A 76* *A 77* *A 78* *A 79* *A 80* *A 81* *A 82* *A 83* *A 84* *A 85* *A 86* *A 87* *A 88* *A 89* *A 90* *A 91* *A 92* *A 93* *A 94* *A 95* *A 96* *A 97* *A 98* *A 99* *A 100* *A 101* *A 102* *A 103* *A 104* *A 105* *A 106* *A 107* *A 108* *A 109* *A 110* *A 111* *A 112* *A 113* *A 114* *A 115* *A 116* *A 117* *A 118* *A 119* *A 120* *A 121* *A 122* *A 123* *A 124* *A 125* *A 126* *A 127* *A 128* *A 129* *A 130* *A 131* *A 132* *A 133* *A 134* *A 135* *A 136* *A 137* *A 138* *A 139* *A 140* *A 141* *A 142* *A 143* *A 144* *A 145* *A 146* *A 147* *A 148* *A 149* *A 150* *A 151* *A 152* *A 153* *A 154* *A 155* *A 156* *A 157* *A 158* *A 159* *A 160* *A 161* *A 162* *A 163* *A 164* *A 165* *A 166* *A 167* *A 168* *A 169* *A 170* *A 171* *A 172* *A 173* *A 174* *A 175* *A 176* *A 177* *A 178* *A 179* *A 180* *A 181* *A 182* *A 183* *A 184* *A 185* *A 186* *A 187* *A 188* *A 189* *A 190* *A 191* *A 192* *A 193* *A 194* *A 195* *A 196* *A 197* *A 198* *A 199* *A 200* *A 201* *A 202* *A 203* *A 204* *A 205* *A 206* *A 207* *A 208* *A 209* *A 210* *A 211* *A 212* *A 213* *A 214* *A 215* *A 216* *A 217* *A 218* *A 219* *A 220* *A 221* *A 222* *A 223* *A 224* *A 225* *A 226* *A 227* *A 228* *A 229* *A 230* *A 231* *A 232* *A 233* *A 234* *A 235* *A 236* *A 237* *A 238* *A 239* *A 240* *A 241* *A 242* *A 243* *A 244* *A 245* *A 246* *A 247* *A 248* *A 249* *A 250* *A 251* *A 252* *A 253* *A 254* *A 255* *A 256* *A 257* *A 258* *A 259* *A 260* *A 261* *A 262* *A 263* *A 264* *A 265* *A 266* *A 267* *A 268* *A 269* *A 270* *A 271* *A 272* *A 273* *A 274* *A 275* *A 276* *A 277* *A 278* *A 279* *A 280* *A 281* *A 282* *A 283* *A 284* *A 285* *A 286* *A 287* *A 288* *A 289* *A 290* *A 291* *A 292* *A 293* *A 294* *A 295* *A 296* *A 297* *A 298* *A 299* *A 300* *A 301* *A 302* *A 303* *A 304* *A 305* *A 306* *A 307* *A 308* *A 309* *A 310* *A 311* *A 312* *A 313* *A 314* *A 315* *A 316* *A 317* *A 318* *A 319* *A 320* *A 321* *A 322* *A 323* *A 324* *A 325* *A 326* *A 327* *A 328* *A 329* *A 330* *A 331* *A 332* *A 333* *A 334* *A 335* *A 336* *A 337* *A 338* *A 339* *A 340* *A 341* *A 342* *A 343* *A 344* *A 345* *A 346* *A 347* *A 348* *A 349* *A 350* *A 351* *A 352* *A 353* *A 354* *A 355* *A 356* *A 357* *A 358* *A 359* *A 360* *A 361* *A 362* *A 363* *A 364* *A 365* *A 366* *A 367* *A 368* *A 369* *A 370* *A 371* *A 372* *A 373* *A 374* *A 375* *A 376* *A 377* *A 378* *A 379* *A 380* *A 381* *A 382* *A 383* *A 384* *A 385* *A 386* *A 387* *A 388* *A 389* *A 390* *A 391* *A 392* *A 393* *A 394* *A 395* *A 396* *A 397* *A 398* *A 399* *A 400* *A 401* *A 402* *A 403* *A 404* *A 405* *A 406* *A 407* *A 408* *A 409* *A 410* *A 411* *A 412* *A 413* *A 414* *A 415* *A 416* *A 417* *A 418* *A 419* *A 420* *A 421* *A 422* *A 423* *A 424* *A 425* *A 426* *A 427* *A 428* *A 429* *A 430* *A 431* *A 432* *A 433* *A 434* *A 435* *A 436* *A 437* *A 438* *A 439* *A 440* *A 441* *A 442* *A 443* *A 444* *A 445* *A 446* *A 447* *A 448* *A 449* *A 450* *A 451* *A 452* *A 453* *A 454* *A 455* *A 456* *A 457* *A 458* *A 459* *A 460* *A 461* *A 462* *A 463* *A 464* *A 465* *A 466* *A 467* *A 468* *A 469* *A 470* *A 471* *A 472* *A 473* *A 474* *A 475* *A 476* *A 477* *A 478* *A 479* *A 480* *A 481* *A 482* *A 483* *A 484* *A 485* *A 486* *A 487* *A 488* *A 489* *A 490* *A 491* *A 492* *A 493* *A 494* *A 495* *A 496* *A 497* *A 498* *A 499* *A 500* *A 501* *A 502* *A 503* *A 504* *A 505* *A 506* *A 507* *A 508* *A 509* *A 510* *A 511* *A 512* *A 513* *A 514* *A 515* *A 516* *A 517* *A 518* *A 519* *A 520* *A 521* *A 522* *A 523* *A 524* *A 525* *A 526* *A 527* *A 528* *A 529* *A 530* *A 531* *A 532* *A 533* *A 534* *A 535* *A 536* *A 537* *A 538* *A 539* *A 540* *A 541* *A 542* *A 543* *A 544* *A 545* *A 546* *A 547* *A 548* *A 549* *A 550* *A 551* *A 552* *A 553* *A 554* *A 555* *A 556* *A 557* *A 558* *A 559* *A 560* *A 561* *A 562* *A 563* *A 564* *A 565* *A 566* *A 567* *A 568* *A 569* *A 570* *A 571* *A 572* *A 573* *A 574* *A 575* *A 576* *A 577* *A 578* *A 579* *A 580* *A 581* *A 582* *A 583* *A 584* *A 585* *A 586* *A 587* *A 588* *A 589* *A 590* *A 591* *A 592* *A 593* *A 594* *A 595* *A 596* *A 597* *A 598* *A 599* *A 600* *A 601* *A 602* *A 603* *A 604* *A 605* *A 606* *A 607* *A 608* *A 609* *A 610* *A 611* *A 612* *A 613* *A 614* *A 615* *A 616* *A 617* *A 618* *A 619* *A 620* *A 621* *A 622* *A 623* *A 624* *A 625* *A 626* *A 627* *A 628* *A 629* *A 630* *A 631* *A 632* *A 633* *A 634* *A 635* *A 636* *A 637* *A 638* *A 639* *A 640* *A 641* *A 642* *A 643* *A 644* *A 645* *A 646* *A 647* *A 648* *A 649* *A 650* *A 651* *A 652* *A 653* *A 654* *A 655* *A 656* 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*A 782* *A 783* *A 784* *A 785* *A 786* *A 787* *A 788* *A 789* *A 790* *A 791* *A 792* *A 793* *A 794* *A 795* *A 796* *A 797* *A 798* *A 799* *A 800* *A 801* *A 802* *A 803* *A 804* *A 805* *A 806* *A 807* *A 808* *A 809* *A 810* *A 811* *A 812* *A 813* *A 814* *A 815* *A 816* *A 817* *A 818* *A 819* *A 820* *A 821* *A 822* *A 823* *A 824* *A 825* *A 826* *A 827* *A 828* *A 829* *A 830* *A 831* *A 832* *A 833* *A 834* *A 835* *A 836* *A 837* *A 838* *A 839* *A 840* *A 841* *A 842* *A 843* *A 844* *A 845* *A 846* *A 847* *A 848* *A 849* *A 850* *A 851* *A 852* *A 853* *A 854* *A 855* *A 856* *A 857* *A 858* *A 859* *A 860* *A 861* *A 862* *A 863* *A 864* *A 865* *A 866* *A 867* *A 868* *A 869* *A 870* *A 871* *A 872* *A 873* *A 874* *A 875* *A 876* *A 877* *A 878* *A 879* *A 880* *A 881* *A 882* *A 883* *A 884* *A 885* *A 886* *A 887* *A 888* *A 889* *A 890* *A 891* *A 892* *A 893* *A 894* *A 895* *A 896* *A 897* *A 898* *A 899* *A 900* *A 901* *A 902* *A 903* *A 904* *A 905* *A 906* *A 907* *A 908* *A 909* *A 910* *A 911* *A 912* *A 913* *A 914* *A 915* *A 916* *A 917* *A 918* *A 919* *A 920* *A 921* *A 922* *A 923* *A 924* *A 925* *A 926* *A 927* *A 928* *A 929* *A 930* *A 931* *A 932* *A 933* *A 934* *A 935* *A 936* *A 937* *A 938* *A 939* *A 940* *A 941* *A 942* *A 943* *A 944* *A 945* *A 946* *A 947* *A 948* *A 949* *A 950* *A 951* *A 952* *A 953* *A 954* *A 955* *A 956* *A 957* *A 958* *A 959* *A 960* *A 961* *A 962* *A 963* *A 964* *A 965* *A 966* *A 967* *A 968* *A 969* *A 970* *A 971* *A 972* *A 973* *A 974* *A 975* *A 976* *A 977* *A 978* *A 979* *A 980* *A 981* *A 982* *A 983* *A 984* *A 985* *A 986* *A 987* *A 988* *A 989* *A 990* *A 991* *A 992* *A 993* *A 994* *A 995* *A 996* *A 997* *A 998* *A 999* *A 1000* *A 1001* *A 1002* *A 1003* *A 1004* *A 1005* *A 1006* *A 1007* *A 1008* *A 1009* *A 1010* *A 1011* *A 1012* *A 1013* *A 1014* *A 1015* *A 1016* *A 1017* *A 1018* *A 1019* *A 1020* *A 1021* *A 1022* *A 1023* *A 1024* *A 1025* *A 1026* *A 1027* *A 1028* *A 1029* *A 1030* *A 1031* *A 1032* *A 1033* *A 1034* *A 1035* *A 1036* *A 1037* *A 1038* *A 1039* *A 1040* *A 1041* *A 1042* *A 1043* *A 1044* *A 1045* *A 1046* *A 1047* *A 1048* *A 1049* *A 1050* *A 1051* *A 1052* *A 1053* *A 1054* *A 1055* *A 1056* *A 1057* *A 1058* *A 1059* *A 1060* *A 1061* *A 1062* *A 1063* *A 1064* *A 1065* *A 1066* *A 1067* *A 1068* *A 1069* *A 1070* *A 1071* *A 1072* *A 1073* *A 1074* *A 1075* *A 1076* *A 1077* *A 1078* *A 1079* *A 1080* *A 1081* *A 1082* *A 1083* *A 1084* *A 1085* *A 1086* *A 1087* *A 1088* *A 1089* *A 1090* *A 1091* *A 1092* *A 1093* *A 1094* *A 1095* *A 1096* *A 1097* *A 1098* *A 1099* *A 1100* *A 1101* *A 1102* *A 1103* *A 1104* *A 1105* *A 1106* *A 1107* *A 1108* *A 1109*

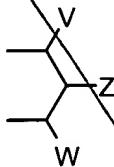
wherein

A is selected from the group consisting of $-\text{NR}^8_2$, $-\text{NHSO}_2\text{R}^3$, $-\text{OR}^5$, $-\text{SR}^5$, halo, lower alkyl, $-\text{CON}(\text{R}^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-\text{NR}^7_2$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

R¹ is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-\text{C}(\text{R}^2)_2\text{aryl}$, $-\text{alk-aryl}$, $-\text{C}(\text{R}^2)_2\text{OC(O)NR}^2_2$, $-\text{NR}^2\text{-C(O)-R}^3$, $-\text{C}(\text{R}^2)_2\text{-OC(O)R}^3$, $-\text{C}(\text{R}^2)_2\text{-O-C(O)OR}^3$, $-\text{C}(\text{R}^2)_2\text{OC(O)SR}^3$, $-\text{alk-S-C(O)R}^3$, $-\text{alk-S-S-alkylhydroxy}$, and $-\text{alk-S-S-S-alkylhydroxy}$, or together R¹ and R¹ are $-\text{alk-S-S-alk-}$ to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R¹ and R¹ are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-\text{R}^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OCOR}^3$, $-\text{CH}_2\text{OC(O)SR}^3$, $-\text{CH}_2\text{OCO}_2\text{R}^3$, $-\text{SR}^3$, $-\text{S(O)R}^3$, $-\text{CH}_2\text{N}_3$, $-\text{CH}_2\text{NR}^2_2$, $-\text{CH}_2\text{Ar}$, $-\text{CH}(\text{Ar})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2\text{R}^2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, and $-\text{R}^2$;

with the provisos that:

a) V, Z, W are not all -H; and

b) when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

R³ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R⁴ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R⁵ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R⁶ is independently selected from the group consisting of -H, and lower alkyl;

R⁷ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and -C(O)R¹⁰;

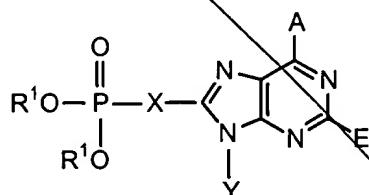
R⁸ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R¹⁰, or together said R⁸ groups form a bidentate alkylene;

R⁹ is selected from the group consisting of alkyl, aralkyl, heteroalicyclic, and alicyclic;

R¹⁰ is selected from the group consisting of -H, lower alkyl, NH₂, lower aryl, and lower perhaloalkyl;

R¹¹ is selected from the group consisting of alkyl, aryl, -OH, -NH₂ and -OR³; and pharmaceutically acceptable prodrugs and salts thereof.

34. (Amended) A method of treating an animal for diabetes mellitus, comprising administering to said animal a therapeutically effective amount of a compound of formula (1):



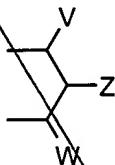
wherein

~~A~~ is selected from the group consisting of $-\text{NR}^8_2$, $-\text{NHSO}_2\text{R}^3$, $-\text{OR}^5$, $-\text{SR}^5$, halo, lower alkyl, $-\text{CON}(\text{R}^4)_2$, guanidino, amidino, $-\text{H}$, and perhaloalkyl;

~~E~~ is selected from the group consisting of $-\text{H}$, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, $-\text{CN}$, and $-\text{NR}^7_2$;

~~X~~ together with ~~Y~~ forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

~~R~~¹ is independently selected from the group consisting of $-\text{H}$, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-\text{C}(\text{R}^2)_2\text{-aryl}$, $-\text{alk-aryl}$, $-\text{C}(\text{R}^2)_2\text{OC(O)NR}^2_2$, $-\text{NR}^2\text{-C(O)R}^3$, $-\text{C}(\text{R}^2)_2\text{-OC(O)R}^3$, $-\text{C}(\text{R}^2)_2\text{-O-C(O)OR}^3$, $-\text{C}(\text{R}^2)_2\text{OC(O)SR}^3$, $-\text{alk-S-C(O)R}^3$, $-\text{alk-S-S-alkylhydroxy}$, and $-\text{alk-S-S-S-alkylhydroxy}$, or together R^1 and R^1 are $-\text{alk-S-S-alk-}$ to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R^1 and R^1 are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-\text{R}^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, alkoxycarboxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, alkoxycarboxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

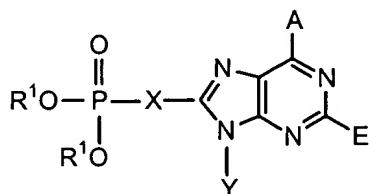
Z is selected from the group consisting of $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OCOR}^3$, $-\text{CH}_2\text{OC(O)SR}^3$, $-\text{CH}_2\text{OCO}_2\text{R}^3$, $-\text{SR}^3$, $-\text{S(O)R}^3$, $-\text{CH}_2\text{N}_3$, $-\text{CH}_2\text{NR}^2_2$, $-\text{CH}_2\text{Ar}$, $-\text{CH}(\text{Ar})\text{OH}$, $-\text{CH}(\text{CH}=\text{CR}^2\text{R}^2)\text{OH}$, $-\text{CH}(\text{C}\equiv\text{CR}^2)\text{OH}$, and $-\text{R}^2$;

with the provisos that:

C 2
cont

a) V, Z, W are not all -H; and
 b) when Z is -R², then at least one of V and W is not -H or -R⁹;
 R² is selected from the group consisting of R³ and -H;
 R³ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;
 R⁴ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;
 R⁵ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;
 R⁶ is independently selected from the group consisting of -H, and lower alkyl;
 R⁷ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and -C(O)R¹⁰;
 R⁸ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R¹⁰, or together said R⁸ groups form a bidendate alkylene;
 R⁹ is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;
 R¹⁰ is selected from the group consisting of -H, lower alkyl, -NH₂, lower aryl, and lower perhaloalkyl;
 R¹¹ is selected from the group consisting of alkyl, aryl, -OH, -NH₂ and -OR³; and pharmaceutically acceptable prodrugs and salts thereof.

35. (Amended) A method of lowering blood glucose levels in an animal in need thereof, comprising administering to said animal a pharmaceutically acceptable amount of a compound of formula (1):



wherein

C2
Cont

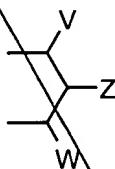
A is selected from the group consisting of -NR⁸, -NHSO₂R³, -OR⁵, -SR⁵, halo, lower alkyl, -CON(R⁴)₂, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -NR⁷₂;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

A24

R¹ is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, -C(R²)₂-aryl, -alk-aryl, -C(R²)₂OC(O)NR², -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, -C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, -alk-S-C(O)R³, -alk-S-S-alkylhydroxy, and -alk-S-S-S-alkylhydroxy, or together R¹ and R¹ are -alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R¹ and R¹ are



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

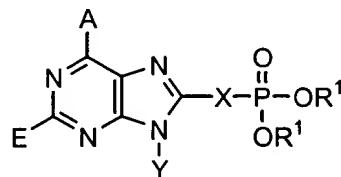
together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR²₂, -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

a) V, Z, W are not all -H; and
 b) when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;
 R^2 is selected from the group consisting of R^3 and -H;
 R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;
 R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;
 R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;
 R^6 is independently selected from the group consisting of -H, and lower alkyl;
 R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;
 R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidentate alkylene;
 R^9 is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;
 R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;
 R^{11} is selected from the group consisting of alkyl, aryl, $-OH$, $-NH_2$ and $-OR^3$; and pharmaceutically acceptable prodrugs and salts thereof.

36. (Amended) A method of inhibiting FBPase at the AMP site in patients in need thereof, comprising administering to said patients an FBPase inhibitory amount of a compound of formula (1):



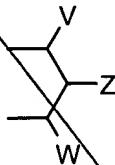
wherein

A is selected from the group consisting of $-NR^8_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

~~E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and -NR⁷₂;~~

~~C2
cont~~
~~X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;~~

~~R¹ is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, -C(R²)₂-aryl, -alk-aryl, -C(R²)₂OC(O)NR²₂, -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, -C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, -alk-S-C(O)R³, -alk-S-S-alkylhydroxy, and -alk-S-S-alkylhydroxy, or together R¹ and R¹ are -alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R¹ and R¹ are~~



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR²₂, -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R³)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- V, Z, W are not all -H; and
- when Z is -R², then at least one of V and W is not -H or -R⁹;

C2 cont

R^2 is selected from the group consisting of R^3 and -H;

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

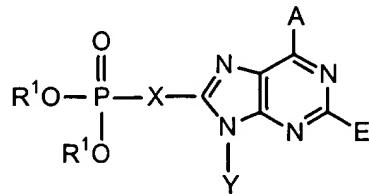
R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidentate alkylene;

R^9 is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-OH$, $-NH_2$ and $-OR^3$; and pharmaceutically acceptable prodrugs and salts thereof.

37. (Amended) A method of inhibiting gluconeogenesis in animal in need thereof, comprising administering to said animal an effective amount of a compound of formula (1):



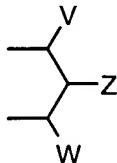
wherein

A is selected from the group consisting of $-NR^{11}_2$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^{11}_2$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

*C 2
Cmt*
R is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$ -aryl, -alk-aryl, $-C(R^2)_2OC(O)NR^2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alk-S-C(O)R³, -alk-S-S-alkylhydroxy, and -alk-S-S-alkylhydroxy, or together R¹ and R¹ are -alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R¹ and R¹ are



V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

- V, Z, W are not all -H; and
- when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

C2
cont

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

A 24
 R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

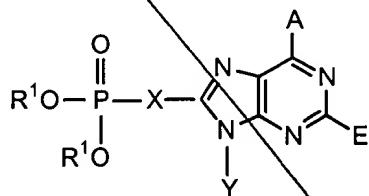
R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidentate alkylene;

R^9 is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-OH$, $-NH_2$ and $-OR^3$, and pharmaceutically acceptable prodrugs and salts thereof.

A 25
39. (Amended) A method of treating an animal for a disease derived from abnormally elevated insulin levels, comprising administering to said animal a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor wherein said inhibitor is a compound of formula (1):



wherein

A is selected from the group consisting of $-NR^{82}$, $-NHSO_2R^3$, $-OR^5$, $-SR^5$, halo, lower alkyl, $-CON(R^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

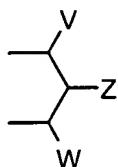
E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-NR^{72}$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

*C 3
cont*

A29

~~R is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, -C(R²)₂-aryl, -alk-aryl, -C(R²)₂OC(O)NR², -NR²-C(O)-R³, -C(R²)₂-OC(O)R³, -C(R²)₂-O-C(O)OR³, -C(R²)₂OC(O)SR³, -alk-S-C(O)R³, -alk-S-S-alkylhydroxy, and -alk-S-S-alkylhydroxy, or together R¹ and R¹ are -alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R¹ and R¹ are~~



wherein

V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and -R⁹; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of -CH₂OH, -CH₂OCOR³, -CH₂OC(O)SR³, -CH₂OCO₂R³, -SR³, -S(O)R³, -CH₂N₃, -CH₂NR², -CH₂Ar, -CH(Ar)OH, -CH(CH=CR²R²)OH, -CH(C≡CR²)OH, and -R²;

with the provisos that:

- V, Z, W are not all -H; and
- when Z is -R², then at least one of V and W is not -H or -R⁹;

R² is selected from the group consisting of R³ and -H;

C 3
cont

A 2 9

R³ is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R⁴ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R⁵ is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R⁶ is independently selected from the group consisting of -H, and lower alkyl;

R⁷ is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and -C(O)R¹⁰;

R⁸ is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, -C(O)R¹⁰, or together said R⁸ groups form a bidentate alkylene;

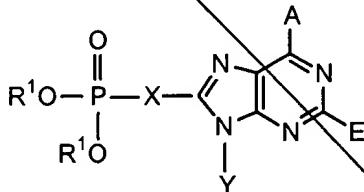
R⁹ is selected from the group consisting of alkyl, aralkyl, , heteroalicyclic, and alicyclic;

R¹⁰ is selected from the group consisting of -H, lower alkyl, -NH₂, lower aryl, and lower perhaloalkyl;

R¹¹ is selected from the group consisting of alkyl, aryl, -OH, -NH₂ and -OR³, and pharmaceutically acceptable prodrugs and salts thereof.

A 2 4

42. (Amended) A method of treating an animal with excess glycogen storage disease, comprising administering to said animal in need thereof a therapeutically effective amount of a fructose-1,6-bisphosphatase inhibitor, wherein said inhibitor is a compound of formula (1):



wherein

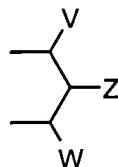
A is selected from the group consisting of $-\text{NR}^8_2$, $-\text{NHSO}_2\text{R}^3$, $-\text{OR}^5$, $-\text{SR}^5$, halo, lower alkyl, $-\text{CON}(\text{R}^4)_2$, guanidino, amidino, -H, and perhaloalkyl;

E is selected from the group consisting of -H, halo, lower alkylthio, lower perhaloalkyl, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, -CN, and $-\text{NR}^7_2$;

X together with Y forms a cyclic group selected from the group of cyclic alkyl, heterocyclic, and aryl;

C4
⑩ w

R^1 is independently selected from the group consisting of -H, alkyl, aryl, heteroalicyclic where the cyclic moiety contains a carbonate or thiocarbonate, $-C(R^2)_2$ -aryl, -alk-aryl, $-C(R^2)_2OC(O)NR^2$, $-NR^2-C(O)-R^3$, $-C(R^2)_2-OC(O)R^3$, $-C(R^2)_2-O-C(O)OR^3$, $-C(R^2)_2OC(O)SR^3$, -alk-S-C(O)R³, -alk-S-S-alkylhydroxy, and -alk-S-S-alkylhydroxy, or together R^1 and R^1 are -alk-S-S-alk- to form a cyclic group, wherein each "alk" is an independently selected alkylene, or together R^1 and R^1 are



V and W are independently selected from the group consisting of hydrogen, aryl, substituted aryl, heteroaryl, substituted heteroaryl, 1-alkenyl, 1-alkynyl, and $-R^9$; or

together V and Z are connected via a chain of 3-5 atoms, only one of which can be a heteroatom, to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus; or

together V and W are connected via a chain of 3 carbon atoms to form part of a cyclic group substituted with hydroxy, acyloxy, alkoxy, alkylthiocarboxy, hydroxymethyl, or aryloxycarboxy attached to a carbon atom that is three atoms from an oxygen attached to the phosphorus;

Z is selected from the group consisting of $-CH_2OH$, $-CH_2OCOR^3$, $-CH_2OC(O)SR^3$, $-CH_2OCO_2R^3$, $-SR^3$, $-S(O)R^3$, $-CH_2N_3$, $-CH_2NR^2$, $-CH_2Ar$, $-CH(Ar)OH$, $-CH(CH=CR^2R^2)OH$, $-CH(C\equiv CR^2)OH$, and $-R^2$;

with the provisos that:

- V , Z , W are not all -H; and
- when Z is $-R^2$, then at least one of V and W is not -H or $-R^9$;

R^2 is selected from the group consisting of R^3 and -H;

C4
Cont
A24

R^3 is selected from the group consisting of alkyl, aryl, alicyclic, heteroalicyclic, and aralkyl;

R^4 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, and lower aryl;

R^5 is selected from the group consisting of lower alkyl, lower aryl, lower aralkyl, lower heteroalicyclic, and lower alicyclic;

R^6 is independently selected from the group consisting of -H, and lower alkyl;

R^7 is independently selected from the group consisting of -H, lower alkyl, lower alicyclic, lower heteroalicyclic, lower aralkyl, lower aryl, and $-C(O)R^{10}$;

R^8 is independently selected from the group consisting of -H, lower alkyl, lower aralkyl, lower aryl, lower alicyclic, $-C(O)R^{10}$, or together said R^8 groups form a bidendate alkylene;

R^9 is selected from the group consisting of alkyl, aralkyl, heteroalicyclic, and alicyclic;

R^{10} is selected from the group consisting of -H, lower alkyl, $-NH_2$, lower aryl, and lower perhaloalkyl;

R^{11} is selected from the group consisting of alkyl, aryl, $-OH$, $-NH_2$ and $-OR^3$; and pharmaceutically acceptable prodrugs and salts thereof.